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Transcription 1

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MH: *It can be made available and transcribed using software so that we can produce a record of it without anyone hitting cues or anything. Why don't you just start by telling me, or listeners in the future, who you are? What your background is? So just a formal who are you?*

PO: Right. Piero Oliaro. I'm Italian. I work for the WHO and I'm on sabbatical for a year with the University of Oxford. So background – infectious diseases, I'm an MD, an infectious diseases specialist and I have been working for the past 25/30 years in tropical medicine …

MH: *Right. Where did you graduate MD?*

PO: In Italy.

MH: *In Italy. Right.*

PO: Yes. And then did a PhD between Italy and France and I've been working for the WHO for the past 22 years.

MH: *22 years. So have you been deployed in various tropical locations all over the world?*

PO: Yes, doing studies all over the world, between Africa, South East Asia, South Asia, Latin America. So I am specifically here for Ebola, I'm part of this team from Oxford.

MH: *When did you get the call to become part of this team?*

PO: I was here just when it happened.

MH: *You were in Oxford?*

PO: Yes. Yes. We got this funding from a grant from the Wellcome Trust to set up a clinical trial platform for Ebola trials. So specifically this one is with a product that's

called TKM and it's got numbers thereafter which keep changing. By this company called Tekmira, Canadian, they have … this product has been … the development of the product has been funded by, essentially, the American DOD, the Department of Defence, and, related to that, there's a number, by the way, of IP issues, both with the product itself, the way it is formulated …

MH: *IP meaning intellectual property.*

PO: Yes, patent protected. By the way, there's a report that's been produced on that, if you're interested I can pass it onto you. And not just this but others as well. So how they have been funded and to what extent they are patent protected. So … but this one in particular is on top of … one of two products on the top of the WHO list of products against Ebola because it has shown not only activity *in vitro* but also in animal models, including the sort of the proof of principle which is in a non-human primate.

MH: *Yes. I read on the website that in non-human primates the protection was 100% when challenged …*

PO: Yes. The important thing is also not just the degree of protection but also when the protection occurs meaning … what they do, they infect the animals and then they treat. So the more effective the product is, the longer the time lag between infection and treatment can be. So a product which is effective when it is given three days after an infection, is more effective than a product that is only effective when it is given on the day.

MH: *On the day.*

PO: And this one is effective when it is given about three days after infection. So that's … probably is the best evidence of efficacy that we can have from animal models, so far, from experimental models.

It's a … what is called a small interfering RNA so it's a molecule, to keep a long story short, that will interfere with viral replication. This is an RNA virus and essentially blocks the replication by blocking the messenger RNAs for some specific molecules, some specific key molecules of this … of the virus, which are three in this case.

MH: *Which are three molecules … right. It's targeting three of the messenger molecules?*

PO: Yes. By the way, the … this mechanism of action, RNA interference, has already been trialled for other diseases but so far, to my knowledge, there is no drug that has been approved …

MH: *By the FDA …*

PO: So that would be the first one. So the complication with these kinds of things is you've got to deliver them so in this case they are trapped within small bubbles which are called nanoparticles which are made of lipids to facilitate them being picked up by cells and then entering into the cells and then matching the RNAs of the virus.

So where are we with that? This was not readily available so had to be produced in a quantity which is large enough to allow for a clinical trial. The product is now available and we have the protocol, we have gone through the ethics approval review, regulatory approval within Sierra Leone for the drug …

MH: *So you fast-tracked the ethical approval?*

PO: It's gone. Done. All the boxes are ticked now and we've got a team already there, ready to start the study.

MH: *So how many doses have you produced and been able to ship to Sierra Leone?*

PO: They produced 100.

MH: *100. 100 therapeutic …*

PO: Yes.

MH: *Right. So that would be enough to …*

PO: To treat 100 patients.

MH: *Right. Right.*

PO: So enough to do a study.

MH: *Right, right.*

PO: And so Peter and I, Peter Horby and I visited Sierra Leone a few weeks ago, just a bit over a month ago and visited sites again and met with investigators and the pharmacy board and the ethics review committee to set things in motion. So essentially we are ready to start and the problem, as you know, at this stage in the epidemic is because it's plummeted. Although there has been a sudden small surge in the number of cases again. But the real challenge at this time, this point in time, is to have enough patients to enrol into a study for the study to be meaningful.

MH: *Yes. Where are these studies going to take place? What hospitals?*

PO: Well, we have a list of them. So we are starting with one … actually they are not hospitals, they are Ebola treatment centres which have been either built on purpose or they have repurposed other places. So we started with one … with the … with an Irish NGO called GOARN …

MH: *Called what? GOARN. How's that spelt?*

PO: [Spells GOARN]

MH: *G-O?*

PO: A-R-N I think.

MH: *Do you know what it stands for?*

PO: We'll find out. Right. And … but there are other places as well that we visited … particularly with government centres as well.

MH: *Are these in and around Freetown as well?*

PO: Well, this one is sort of up country within or around a couple of hours drive or less …

MH: *What district is it in? Can you remember? Maybe you can …*

PO: It's in Port Loko.

MH: *Where?*

PO: Port Loko.

MH: *Port Loko, okay.*

PO: But our counterparts, locally, so the local investigators are the commerce of medicine which are called the Cohmas, [spells Cohmas]

MH: *Cohmas?*

PO: Yes.

MH: *College of Medicine.*

PO: And applied health sciences.

MH: *Right. Who is the lead investigator or director of that?*

PO: It's Doctor Samai but I will give you all the details.

MH: *Okay. Okay. Because I think it's quite important for me to also talk to African …*

PO: Absolutely. By all means. You have to talk to … by all means. And I can give you a list of the names of people to talk to.

MH: *That would be great, yes.*

PO: And by the way, if you're going now, you'd have somebody there who's the sort of lead investigator in the country from here which is … whose name is Jake Dunning.

MH: *Jake Dunning, yes. I actually have already made contact with him by Twitter …*

PO: Okay. So he'll be there. He'll be …

MH: *He's going to be there in March?*

PO: Yes, yes, he's there now. He's there now.

MH: *Okay, so he's the lead investigator …*

PO: Locally. So he's the sort of clinical coordinator in the country for us.

MH: *That will be very useful, yes. Right. I mean, lots and lots of questions but just to talk about this trial and the principles so … the idea of doing a trial of a therapeutic*

drug or even a vaccine whilst an epidemic is going on, hasn't been tried very often, has it?

PO: No, but it's the only way of doing it, no? So you can't do it otherwise.

MH: *No but what I'm asking is, it's very unusual kind of research to undertake, right … it must bring all sorts of challenges.*

PO: All sorts of challenges, right, like you say … of course because you have both the challenges of a clinical trial that has to follow the international regulations of GCPs – good clinical practices and everything in order for it to be used further down the line for registration. But you have the challenges of doing that in an emergency situation, plus the challenges of doing that with a disease that can be highly contagious when it comes to the patients with symptoms and sick people. And all the [? 13:21] of that, so challenges … you just name it, there's no shortage of the challenges. So you've got …

MH: *Can I ask, where there any models for this sort of study that you could base … I suppose the model would be the standard model for doing a trial …*

PO: That's it, yes. That's against the background of something that already exists of course. So there's an issue about … so, again, models are … all the rules and regulations are for GCP and regulatory authorities demand. So that's one thing. The other thing is … so that's there and, of course, it's got to be adapted in the situation locally. The second model is the different types of study design and in this case we used … we adapted the trial design which allows you to …essentially to answer questions minimising the number of patients exposed and shortening the time that it requires to get that answer. And, again, I can give you details about the study design and everything. So these are the sort of models.

Now, the models that do not exist, and you have to sort of … to … finding out as you go along, are how to do all that in these two very special circumstances which are an epidemic, meaning it's not true any more but just a few months ago these places were over-crowded and the health providers there were just overwhelmed by the number of cases and all the pressures … pressure they are under. The second one is you have got to do it safely for the … your personal staff, for the staff. And the third one is, of course, that the people … the patients there … it may be … it may be very difficult for them to understand what's going on either because they are kids or, of course, they are very sick so …

MH: *You said because they are kids … oh, children?*

PO: Children. So … and it may be difficult for them to understand. It's a problem … language barrier, of course, you need translation but they may be so sick it's very difficult for them to understand. To have … to do that, informed consent has been a big issue that we debated. Plus all the, you know, the details of how do you do things. It gets very difficult even to get … to talk to a person when you are wearing PPE and a mask and goggles or a … or whatever. You're not even human, you're

not a human being that they're talking to. It must be very intimidating plus being sick due to Ebola.

So a whole range of challenges and actually we are going to write it up in a paper for reference because, like I say, there's a number of obstacles and challenges all along and even after you've started the study, you think you've got all of your standard operating procedures, SOPs, in place. Yet you discover that it doesn't fit all the time, there are always some special cases.

MH: *Right. So you are constantly having to adapt to the situation confronting you.*

PO: Yes. And hopefully you're getting it right, of course, so you have to … it's very challenging indeed, yes.

MH: *Did you yourself, when you were in Sierra Leone … you visited some of the centres and saw …*

PO: Of course, yes.

MH: *Right. So were you … in order to sort of find the right place to do the trial, did you have to put suits on and go …*

PO: Of course, yes.

MH: *Can you just describe briefly what that procedure involved when you're trying to decide is this an appropriate place for a trial? What were you looking for?*

PO: Okay, we have a list, a sort of check list that we go through, if you're interested in, we can provide it of course … but we're also supposed to be writing a paper but the problem is time, as always, lack of thereof rather. So, in terms of suitability, there are many criteria. Of course, having patients is one but of course this might change with time.

MH: *But in terms of … let's just start with the logistics. In order … what things have to be present in this Ebola treatment centre for the trial to work effectively?*

PO: Right. So the layout, the way it is set up or whether it is conducive for doing study, if it is a mess, if it is just a sort of cluster of tents or if it is well-organised. Of course that's very important. So the way it is … the day to day function of the centre we have to look at – are they well organised, do they have different things? And then things like having a pharmacy, having a well-defined protocol for admitting patients, screening patients, looking after patients and so on and so forth. Whether they've got a lab where tests can be done. How efficient the system is. Essentially all these kind of things.

And then there's a long list of things to check and then of course you talk to people, you try to understand how they function, how stable the operation is. Personnel are rotating or not …

MH: *Just because I want to understand, in this sort of trial, unlike a vaccine trial, you don't have a placebo control group?*

PO: You could. If you wanted to but specifically with our trial design we don't, we base our assumptions on case fatality rates right before the trial starts, at that site, in order to be able to offer potentially effective treatment to all patients as opposed to analysing them to whatever they are getting today.

MH: *So that means it's important at the site you choose that they have good laboratory diagnostics in place.*

PO: Yes.

MH: *Before you even start the trial.*

PO: Yes, of course. Then, of course, one of the things that, in this specific case, has not been done in the past … throughout everywhere and across all sites, there's been very little I would say basic clinical medicine done. For instance we … until very recently blood samples have not been taken to check basic liver function, renal function tests, those are the sort of things which of course you'd be doing here. So we … as a matter of fact, we have very little information about these very basic elements …

MH: *Because you need to know as much as you can about the patient's state of health beside the fact they have Ebola.*

PO: Yes, the problem is probably there must be around about 23,000 cases which have been confirmed and suspected so far. So I don't know what proportion of them has been treated in centres – I'd say probably more than 10,000 or 15,000 and all those tens of thousands of patients we have no information about their liver functions or renal functions.

MH: *Or indeed if they've been co-infected with something like another virus like malaria.*

PO: Well we sort of do know that for a proportion of them. And be it as it may, practice has been to give an anti-malarial anyway to all patients. So sort of benefit of doubt, sort of general practise has been to give patients anti-malarials and anti-bacterials … so antibiotics, so a sort of broad spectrum coverage between malaria and common microbes. So that is what has been … of course, mostly because also patient investigations have not been done … the reason this has not been done is

sort of two-fold. One is that because every time you take a blood sample you expose your personal staff to a risk, not only when the sample is drawn but when it is put through the machine, as it were. So this is one. The other one is that for some very weird reason people thought that was not needed … and even people in this country who have been telling … saying … who have been saying that was research …

MH: *Sorry, I'm going to have to stop this. The background noise is just unbelievable …*

PO: I'm sorry.

MH: *Sorry. Hang on, let me just. Oops. I wonder if we can go somewhere else a bit quieter …*

END OF RECORDING